REMARKS

Amendments

Claims 1 and 30 are amended to expressly describe "analogue" in accordance with the description in the specification. See, e.g., page 27, lines 7-23. In addition, claim 1 is amended to eliminate the term "chain" form the description of the substituted carbonyl group. Also, claims 20, 27 32, and 33 are amended to correct obvious typographical errors.

Rejection Under 35 USC §112, second paragraph

As discussed previously, contrary to the assertion in the rejection, the term "analogue" in the contest of nucleoside bases is not indefinite. Applicants describe in their specification the types of structures included within this. See, e.g., the various listings of bases for group B in the specification. See also the discussion of "analogue" at page 27, lines 7-23. One of ordinary skill in this art can readily recognize whether a compound exhibits a purine or pyrimidine analogue structure. Claims 1 and 39 now expressly recite the description of analogue in accordance with the discussion of "analogue" at page 27, lines 7-23.

The term "carbonyl substituted by..." is sufficiently definite. One of ordinary skill in the art would understand that straight, branched and cyclic refer to the alkyl group, rather than, for example, simply straight chain or branched chain. The rejection presents no rationale as to why one would interpret the claim in this unreasonable manner. In any event, the description of Ra is amended to delete the unnecessary term "chain."

Finally, as noted above, claims 32 and 33 are amended to correct obvious typographical errors. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 USC §103

Claims 1-40 are rejected as allegedly being obvious in view of Mikhailopulo et al. in view of Brillanti et al. and Matthes et al. Applicants respectfully traverse.

Mikhailopulo et al. disclose the results of a study on the synthesis and some biological properties of certain 3'-fluoro-3'deoxyribo-nucleosides and 2'-derivatives thereof. Beginning at page 2198, right column, the biological activities listed in Table IV are discussed. Compounds

34a, 34b, 35a, and 35b were found to have no significant activity against any of the viruses tested at sub-toxic concentrations. On the other hand, compound 26 was some to have markedly inhibitory activity against some of the viruses tested, although its toxicity was also high. Compounds 23 and 25 were shown to be marginally active against some of the viruses that were sensitive to compound 26.

It is undeniable that Mikhailopulo et al. provide no biological data on inhibition of HCV for any of the compounds in the study. In fact, Mikhailopulo et al. do not even discuss HCV. But, in the rejection, it is argued that Mikhailopulo et al. provide data for some of the compounds for the inhibition of certain (+)RNA viruses. Based on this disclosure, it is alleged that it would be obvious to treat other (+)RNA viruses with these compounds, including hepatitis C virus.

However, the rejection presents no rationale as to why one of ordinary skill in the art would conclude that simply because a compound exhibits inhibition activity against one (+)RNA virus that it would be reasonable to conclude that it is active against all (+)RNA viruses. In fact, the data presented by Mikhailopulo et al. show that the general premise relied on in the rejection is incorrect. In Table IV compounds 23 and 25 are shown to have some marginal activity against the (+)RNA viruses polio and Coxsackie (picorna viruses) and Sindbis (a toga virus). But, they were both inactive at sub-toxic concentrations against Semliki forest virus, another (+)RNA toga virus. Moreover, none of the (+)RNA viruses tested by Mikhailopulo et al. were of the Flavivirdae family, the family of viruses to which HCV belongs. See also the enclosed excerpt from *Virology*, 2nd Edition, edited by B. N. Fields (Raven Press, New York, New York) which states that Flavivirdae is classified as a separate family of viruses from the Togaviridae family of viruses.

In the rejection, it is argued that it would be obvious to use a nucleoside of Mikhailopulo et al. in combination with IFNα, based on the disclosure of Brittanti et al. However, while Brittanti et al. note that IFNα in combination with oral ribavirin is "considered the best therapy" for patients who are infected with HCV and are non-responsive to IFNα, their results on the use of this combination for retreatment was disappointing. See page 133, left column, second full paragraph and page 133, right column, last sentence of first paragraph.

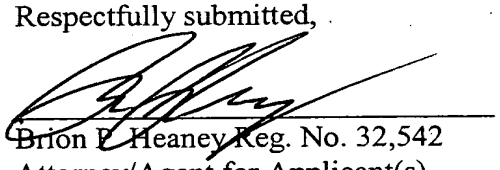
The rejection further relies on Matthes et al. for the disclosure of a treatment Rauscher murine leukemia using FTdR (2',3'-didexoy-3'-fluorothymidine) at a dosage of 69 mg/kg/day. Yet, Matthes et al. provide no disclosure of the treatment of HCV infections or suggest what

dosages one would use for such treatment.

In view of the above remarks, it is respectfully submitted that Mikhailopulo et al., alone or in combination with Brittanti et al. and/or Matthes et al., fails to provide sufficient motivation to lead one of ordinary skill in the art to modify the disclosure of Mikhailopulo et al. so as to arrive at an embodiment in accordance with applicants' claimed invention. Thus, it is respectfully submitted that Mikhailopulo et al., alone or in combination with Brittanti et al. and/or Matthes et al., fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Date: January 2, 2004.

Virology, Second Edition, edited by B. N. Fields, D. M. Knipe et al. Raven Press, Ltd., New York © 1990.

CHAPTER 25

Replication of Togaviridae and Flaviviridae

Sondra Schlesinger and Milton J. Schlesinger

The family of Togaviridae was originally composed of several genera including alphaviruses, flaviviruses, and rubiviruses (101). These viruses had been grouped together based on size, on their having a single-strand nonsegmented RNA genome that functions as a messenger RNA, and on the ability of many of the members to replicate in and be transmitted by mosquitos. Studies on the structure of the genomes and on the replication strategies of these viruses made it clear that flaviviruses were distinct from the other members and they are now classified as a separate family, the Flaviviridae. Historical precedent keeps these two families together, and this chapter provides a brief review of the structure and replication of prototype members of both; more detailed information can be found in ref. 117.

TOGAVIRUSES

Togaviruses are among the most simple enveloped animal viruses. Their genome consists of a single strand of RNA of positive (+) polarity that is encapsidated by a single species of protein (the capsid protein) arranged in an icosahedral configuration with T = 3 symmetry (43) (see Chapter 3). This nucleocapsid is enveloped by a lipid bilayer derived from the host-cell plasma membrane. Projecting from the bilayer and embedded in it are the viral-encoded glycoproteins designated as E1 and E2. They are arranged such that three heterodimers form a trimer spike. Eighty of these spikes are arranged on a T = 4 icosahedral axis (see Chapter 3).

Alphaviruses and rubiviruses are two genera in the togavirus family. The third genus, the pestiviruses, includes the mucosal disease viruses, bovine diarrhea virus, and hog cholera virus. The structure and replication of the two alphaviruses, Sindbis (SIN) and Semliki Forest virus (SFV), have been studied in great detail and these viruses have provided valuable models for examining the synthesis, posttranslational modifications, and localization of membrane glycoproteins. Other alphaviruses including the equine encephalitis viruses and Ross River virus have been noted for their ability to cause natural infections and disease in animals and humans (see Chapter 26). The sole member of the rubivirus genus, rubella virus, is well known for its ability to cause disease in humans.

Alphaviruses

Structure of the Genome

The complete sequence of the SIN and SFV genomes has been determined (46,47,102,132,141), and partial sequence information is available for several other alphaviruses (24,29,133). The genomes contain approximately 11,700 nucleotides; the 5′ ends are capped with a 7-methylguanosine, and the 3′ ends are polyadenylated. During replication, a discrete subgenomic mRNA species (referred to as 26S RNA) is formed. The subgenomic RNA contains approximately 4,100 nucleotides identical in sequence to the 3′-terminal one-third of the genomic RNA (see Fig. 2). This

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